Prevalence of risk-drinking in critically ill patients, screened with carbohydrate-deficient transferrin and AUDIT-C score : A retrospective study

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Prevalence of risk -drinking in critically ill patients, screened with carbohydrate-deficient transferrin and AUDIT-C score: a retrospective study

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Competing interest

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Abstract

Background: Studies demonstrate that up to one-third of intensive care unit (ICU) admissions are directly or indirectly related to alcohol. Screening for alcohol use is not routine. This study examined the prevalence of elevated %CDT (carbohydrate-deficient transferrin) and above risk-level AUDIT-C (Alcohol Use Disorders Identification Test, Consumption) in patients admitted to ICU.

Methods: We conducted a retrospective analysis of clinical and laboratory data from a single ICU where %CDT and AUDIT-C were included in routine assessment. After excluding readmissions, 2532 adult patients from a 21-month period were included. Admission values of %CDT were available for 2049 patients, and AUDIT-C was available for 1617 patients. The association of %CDT and AUDIT-C with short- and long-term outcome was studied by using univariate and multivariate logistic regression analysis.

Results: %CDT was above the reference value in 23.7% (486/2048) of patients with available %CDT. Of patients with available AUDIT-C, 33% (544/1617) had a risk-level AUDIT-C score. Patients with a risk-level AUDIT-C score were significantly younger than those with a lower score (51 vs. 64 years, $p<0.0001$). Increased %CDT was associated with higher severity of illness. AUDIT-C was associated independently with increased risk of long-term mortality in multivariate analysis ($p=0.007$).

Conclusion: One in three of ICU patients are risk-level alcohol users as measured with AUDIT-C score, and one in four analysed with %CDT. The prevalence varies according to the method used and any method alone may be insufficient to detect risk-level consumption reliably.

Editorial Comment:

Alcohol overconsumption is associated with need for ICU admission and also with less favourable outcomes. Diagnosis of alcohol overconsumption though is problematic due to low sensitivity in

screening. In a pilot study, a biomarker and a screening tool are compared. The finding is that multiple tools are needed to achieve an adequate sensitivity for detection.

Introduction

Harmful alcohol use is a global problem with negative health, social and economic consequences, and it is a causal factor in many diseases and injuries [1]. Previous studies suggest that up to one third of intensive care unit (ICU) admissions are directly or indirectly related to alcohol use [2-5]. Patients with a history of harmful alcohol use have an increased risk for complications [6-10]. Data on the association of harmful alcohol use with mortality are contradictory [3-5, 11, 12].

World Health Organization (WHO) divides risk drinking in the following four categories: low risk (1 to 20 g per day for females / 1 to 40 g per day for males), medium risk (21 to 40 g per day for females / 1 to 40 g per day for males), high risk (41 to 60 g per day for females / 61 to 100 g per day for males), or very high risk (61 g or more per day for females / 101g or more per day for males)[13]. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines recognizes moderate alcohol consumption as one standard drink per day for women and no more than two standard drinks per day for men[14]. Screening for risk-level alcohol use is usually based on self-report. Questionnaires are screening tools for detecting alcohol use that exceeds a level where risk for alcohol-related problems increases [15]. Alcohol Use Disorders Identification Test (AUDIT) is a validated screening tool for risk-level alcohol use [16, 17]. The short version, AUDIT-C (for details, see Additional File 1), includes questions about alcohol consumption. It consists of items 1 to 3 of the full AUDIT, with a total score ranging from 0 to 12 points [18]. In the Finnish population, the AUDIT-C lower limit cut-off point for risk -drinking is 5 for women and 6 for men [19, 20].

However, self-report commonly leads to an underestimation of daily alcohol consumption [21], and critical illness may challenge patients´ ability to communicate. Alternative methods to identify acute and chronic use of alcohol include several laboratory tests, such as the enzymes gamma-glutamyltransferase (GGT) and, alanine and aspartate aminotransferase (ALT, AST) and the mean corpuscular volume of erythrocytes (MCV). A limitation of these tests is their poor specificity for harmful use of alcohol [22].

Carbohydrate-deficient transferrin (%CDT), the percentage of desialylated transferrin of total transferrin concentration) is the most commonly used biomarker to identify chronic alcohol use

in outpatient healthcare (elevations of %CDT requires consumption of 50-80g ethanol per day, at least two weeks[23]). It has high specificity but low sensitivity [24]. Reported sensitivity varies widely in different clinical settings, from 32% to 96%, and specificity from 63% to 100% [25]. In primary care, a cut-off value of 2.5% or even 3.0% has been proposed for both sexes [26-28]. Recently, clinical laboratories in Finland have set a cut-off level of 2.5% desialylated transferrin of total transferrin concentration for detecting harmful alcohol consumption.

The aim of our study was to evaluate the prevalence of increased %CDT in critically ill patients in a mixed ICU. In addition, we explored its association with length of ICU treatment and outcome measures. Another aim was to evaluate the correlation of %CDT with AUDIT-C, ALT, and MCV. We also studied the prevalence of risk-level AUDIT-C and its association with outcome.

Patients and methods

The study population of this retrospective study included patients treated in the ICU of Tampere University Hospital between December 9th, 2011 and September 8th, 2013. The Tampere University Hospital ICU is a 24-bed mixed unit in a tertiary hospital. Data were obtained from the national intensive care quality database (Intensium, Tieto OY, Finland) and hospital laboratory records. Authorization for using the clinical and laboratory data was granted by Tampere University Hospital. Due to the retrospective non-interventional study design the need for obtaining informed consent was waived.

The 21-month period was chosen because during that time period %CDT was included in the routine admission laboratory test package. We included only adult patients (age ≥ 18 years) and excluded data from readmissions, with the exception of AUDIT-C scores if they were not available in the index admission (n=33). This was considered justified because AUDIT-C reflects long-term alcohol consumption and was not expected to change over the hospital admissions. AUDIT-C was routinely scored in the ICU when possible.

The following data were recorded: age, sex, admission type (emergency vs. elective and operative vs. non-operative), ICU primary diagnosis according to the *International Classification of Diseases,* 10th edition (ICD-10), Acute Physiology and Chronic Health Evaluation II (APACHE II)

scores, Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score within the first 24 hours of ICU admission, Therapeutic Intervention Scoring System (TISS), and ICU- and hospital mortalities. Dates of death were obtained from Statistics Finland, and three-year mortality was calculated. Admission %CDT (carbohydrate-deficient transferrin), ALT (alanine aminotransferase). and MCV (mean corpuscular volume of erythrocytes) were registered when available. Laboratory analyses were performed in Fimlab Laboratories Oy Ltd, according to IFCC (International Federation of Clinical Chemistry and Laboratory Medicine). %CDT was analysed by using nephelometry method. We searched the national intensive care quality database for obtaining all ICD-10 codes, including the alcohol-related diagnoses that have been certified for registering alcohol-related deaths in the Official Statistics of Finland (for details, see Additional File 2).

For statistical analyses, we used IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). We calculated the prevalence of elevated %CDT and/or risk-level AUDIT-C scores, the correlation of %CDT and AUDIT-C scores with ALT and MCV, and their association with survival. Continuous variables are expressed as medians and interquartile ranges, and if non-normally distributed, compared using the nonparametric Mann-Whitney U- or Kruskal-Wallis test. Categorical data are presented as absolute numbers and percentages and compared using Chi-square or Fisher´s exact test. Spearman's rank correlation test was used to analyze the correlation of %CDT with other laboratory variables and AUDIT-C scores. Finally, we used stepwise backward logistic regression analysis to test the independent association of the studied variables with mortality. The variables were selected to the multivariate analysis if p was <0.2 in univariate analysis. In all other analyses, we considered $p<0.05$ to be statistically significant.

Results

A flow-chart of patients evaluated and included in the final analyses is shown in Figure 1.[3]

Patient characteristics

Of the study population, 63.4% (n=1607) were men. The median age of all patients was 60 [45-70] years. Of the 2532 study patients 7.9% (n=200) had an alcohol-related ICD-10 diagnosis. Table 1 shows the patient characteristics and clinical measures in groups defined by whether the admission %CDT values and AUDIT-C scores were available or not. Table 2 and Supplementary Table 1 show study population characteristics by using AUDIT-C reference values for Finnish women and men, and outpatient reference values for %CDT. Figures 2a and 2b show %CDT distribution for women and men by using AUDIT-C reference values. [4]

Correlation of %CDT with AUDIT-C and their correlations with other laboratory values

Spearman's rank correlation coefficient for %CDT with AUDIT-C scores was 0.282 (n=492, p<0.001) for women and 0.480 (n=850, p<0.001) for men. A significant albeit weak correlation of %CDT with ALT (r_s=0.144, n=1961, p<0.001) and MCV (r_s=0.185, n=2043, p<0.001) was present. Spearman´s rank correlations of AUDIT-C scores with ALT and MCV were 0.233 (n=1499, p<0.001) and 0.199 (n=1606, p<0.001), respectively.

Association of %CDT and AUDIT-C with survival

Elevated %CDT or AUDIT-C scores were not significantly associated with increased ICU mortality in univariate analyses. Median %CDT was significantly higher in hospital non-survivors and 3-year non-survivors. Median AUDIT-C scores were significantly higher in 3-year survivors than in non-

[3] Figure 1
[4] Table 1, Supplementary Table 1, Table 2, Figure 2

survivors. Results of the univariate comparisons are shown in Table 3. We performed a sensitivity analysis where we excluded patients who had been discharged alive in less than 24 hours from the ICU to control for the effect of very low mortality in intoxicated patients who tend to stay only for a short time in the ICU. However, despite excluding these patients, the association with mortality did not change. Adjusted for age and severity scorings, AUDIT-C was associated with increased odds of 3-year mortality (1.060 [1.016-1.105], p=0.007). Multivariate logistic regression analyses are shown in Supplementary Table 2. [5]

[5] Table 3, Supplementary Table 2

Discussion

In this retrospective observational study, we investigated the prevalence of risk-level alcohol use with two different measures, elevated %CDT and risk-level AUDIT-C scores, in patients admitted to a medical-surgical ICU. By using the reference values validated for outpatient care, we found that the resulting prevalence of patients with alcohol risk -drinking differed according to the method used. At admission, %CDT was increased in 23.7% of the patients. Risk-level AUDIT-C scores were seen in 33.6% of the patients with available AUDIT-C scores. Despite the different results according to the method, our results were quite similar to those reported by others. The prevalence of risk-level AUDIT-C scores in our study was the same as in a previous study where questionnaires had been used for screening risk-level alcohol use [5, 8]. Concerning the prevalence of elevated %CDT, we found that %CDT was increased more often than in another study where a prevalence of 19% was reported for trauma patients [29].

AUDIT-C scores were not associated with severity of illness, organ failures, or therapeutic intervention scores. By contrast, patients with increased %CDT did have higher SAPS II, SOFA 24, and TISS scores than patients with %CDT within the reference range. Acute-phase reactions have an influence on the secretion and synthesis of sialic acid [30], which can partly explain our findings of higher scores of disease severity and intensity of care for patients with elevated %CDT. However, the link between severity of illness and elevated %CDT is unclear. For example, alcohol-induced %CDT could represent a physiological state, that leads to a more severe illness. It has been shown that risk-level alcohol use increases the risk for postoperative complications and acute respiratory distress syndrome [9, 31]. One explanation for this discrepancy between the two measures could be the slightly different populations. While CDT was ordered as a part of the routine admission laboratory package, obtaining AUDIT-C requires discussion with either the patient or a relative. Hence, patients with available AUDIT-C score may have survived longer or maintained better cognition than patients with available %CDT. This is naturally a source of selection bias in our results.

Previous studies have demonstrated that CDT is quite specific, but lacks sensitivity in detecting harmful alcohol use [25]. Risk of false-positive CDT has been reported in many conditions [24, 32, 33]. Among other factors, female gender has been associated with reduced diagnostic sensitivity of %CDT[34]. This is in broad accordance with our results, as the correlation of AUDIT-C with %CDT was lower in female patients in our study. Because of such limitations, CDT is recommended for use in combination with other measures such as GT [24, 35-38]. In our study, there was a statistically significant but weak correlation of %CDT and AUDIT-C scores with other biomarkers that have been used in screening for risk-level alcohol consumption. Recently, new biomarkers, such as phosphatidylethanol (PEth) have come on the market. PEth is a direct alcohol biomarker, which, according to a recent study, seems promising in distinguishing harmful alcohol use in critically ill patients, showing good diagnostic accuracy [39].

AUDIT-C has been demonstrated to be a useful screening instrument in general hospital settings and in trauma patients [40, 41]. The use of questionnaires in screening is non-invasive, inexpensive, and fast. However, self-report in critically ill patients may be hindered by impaired communication when the patient is acutely admitted and severely ill. In such situations, a recent outpatient AUDIT-C score or a relative´s estimate of the patient´s alcohol consumption can be used. Because of the limitations of the self-report, any laboratory test that objectively identifies the acute and/or chronic use of alcohol in critically ill patients is desirable. Validated codes, such as ICD-10 codes for alcohol-related diagnoses, have been reported to underestimate the prevalence of harmful alcohol use [42]. This was obvious also in our study; %CDT was increased and AUDIT-C scores were above the recommended risk limits more often than an alcohol-related diagnosis was present. On the other hand, it is reasonable to assume that a diagnosis would be more likely to be registered in the ICU data management system, if an indicator of alcohol risk - drinking, such as %CDT or AUDIT-C score, was available.

Patients with risk-level %CDT or AUDIT-C were younger and more often male than other critically ill patients. This is in agreement with earlier studies that have also shown that patients with alcohol-related ICU admissions are younger and most often male [3, 4, 12]. In our study, neither increased %CDT nor risk-level AUDIT-C scores were associated with a longer ICU stay. This is

consistent with the findings of Fleming et al. [43], but contradicts another study, where high CDT levels were associated with a prolonged ICU stay [29, 44]. In our study, %CDT and AUDIT-C were not associated with an increased risk of ICU or hospital mortality. When adjusted for age and severity scores, AUDIT-C was independently associated with poorer long-term survival, similarly as reported by others [5]. In another large retrospective study, patients with complications of alcoholism, such as alcohol liver disease, had increased short- and long-term mortality. In that study, population alcohol-related diagnoses were not associated with increased short-term mortality, which is in broad agreement with our result. There was only slight evidence of increased long-term mortality among patients without complications of unhealthy alcohol use [11].

Currently, to our knowledge, alcohol use among ICU patients is not screened routinely in many countries. In our study, the prevalence of risk-level alcohol use varied depending on the screening methods used. However, our study corroborated previous findings that risk-level alcohol use is a highly prevalent background lifestyle factor among ICU patients. In earlier studies, unhealthy alcohol consumption has been shown to be a risk factor for such complications as ICU-acquired bacterial infection, acute respiratory distress syndrome, and septic shock [8, 9, 45]. Although we did not have data to examine the direct association with such complications, we agree that unhealthy alcohol consumption as an anamnestic factor warrants attention. Special efforts in recognizing patients with risk-level alcohol use should be made to enable preparation for complications and, importantly, to initiate interventions to help patients modify their behavior. Serious illness can be a good opportunity to support patients in their decisions to change unhealthy lifestyle factors.

Our study has some limitations. First, the study was retrospective and performed in a single center with a high representation of neurological and neurosurgical patients. Second, the available patient populations with AUDIT-C and %CDT were not identical and conditions for obtaining each variable may have been different, causing selection bias and affecting the generalizability of our results. Third, we did not have sufficient data to compare %CDT with other alcohol-associated laboratory markers such as GT or PEth. Fourth, lack of a gold standard in detecting unhealthy alcohol consumption reliably in a retrospective setting prevented us from analyzing the diagnostic accuracy of %CDT and AUDIT-C. Our study also has some strengths. It is

the first study to explore %CDT in a mixed ICU population. Earlier studies of %CDT and critically ill patients have included only trauma patients. To our knowledge, this is the largest study on the prevalence of increased %CDT and risk-level AUDIT-C, reporting also their association with outcome measures in critically ill patients.

Conclusions

Risk-level alcohol consumption is a lifestyle factor that is present in a significant proportion of intensive care patients. The prevalence varies according to the screening method used and any method alone may be insufficient to detect risk-level consumption reliably. In this study we were unable to show an association of alcohol -use disorder with short-term patient outcomes, but AUDIT-C was independently associated with long-term outcome.

List of abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test, -Consumption
CDT	Carbohydrate-deficient transferrin
GGT	Gamma-glutamyltransferase
ICD-10	International Classification of Diseases, 10th edition
ICU	Intensive Care Unit
MCV	Mean corpuscular volume of erythrocytes
PEth	Phosphatidylethanol
SAPS II	Simplified Acute Physiology Score II
SOFA	Sequential Organ Failure Assessment score

TISS Therapeutic Intervention Scoring System

References

Table 1. Study population characteristics according to availability of %CDT and AUDIT-C.

	Both %CDT and AUDIT-C score available (n=1342)	Only AUDIT-C score available (n=275)	Only %CDT available (n=706)	%CDT and AUDIT-C score not available (n=209)	p value
Age (years)	58.0 [42.0-68.0]	65.0 [52.0-74.0]	61.0 [47.0-71.0]	66.0 [53.0-76.0]	p<0.001*
Sex (men)	850 (63.3%)	174 (63.3%)	447 (63.3%)	134 (64.1%)	p=0.997
Emergency admission	1282 (95.5%)	223 (81.1%)	665 (94.2%)	190 (90.9%)	p<0.001*
Operative	209 (15.6%)	105 (38.2%)	146 (20.7%)	63 (30.1%)	p<0.001*
SAPS II	30.0 [20.0-43.0]	35.0 [24.0-46.0]	38.0 [24.0-57.0]	49.0 [30.0-66.5]	p<0.001*
SOFA 24	5.0 [3.0-8.0]	6.0 [4.0-10.0]	7.0 [4.0-10.0]	9.0 [5.0-11.8]	p<0.001*
TISS sum	65.0 [40.0-125.0]	88 [52.0-164.0]	64.5 [43.0-121.0]	72.0 [38.3-119.0]	p<0.001*
ICU LOS (days)	1.48 [0.78-3.11]	1.84 [0.91-3.87]	1.15 [0.67-2.64]	0.99 [0.58-2.54]	p<0.001*
Alcohol-related diagnosis	118 (8.8%)	10 (3.6%)	57 (8.1%)	15 (7.2%)	p=0.036*
ICU mortality	27 (2.0%)	9 (3.3%)	85 (12.0%)	59 (28.2%)	p<0.001*

Continuous variables are expressed as medians and interquartile ranges [IQR] and compared between groups shown in the table using the Kruskal-Wallis test. Categorical data are presented as absolute numbers and percentages and compared using the Chi-square test.

%CDT, carbohydrate-deficient transferrin; AUDIT-C, Alcohol Use Disorders Identification Test, Consumption; SAPS II, Simplified Acute Physiology Score II; SOFA 24, Sequential Organ Failure Assessment score after first 24 hours in the ICU; TISS, Therapeutic Intervention Scoring System; ICU LOS, Intensive Care Unit Length of Stay.

Table 2. %CDT and AUDIT-C values in different groups according to primary diagnosis in ICU.

Diagnostic category n(%)	**AUDIT-C scores <5♀, <6 ♂ (n=1073)**	**AUDIT-C score ≥ 5♀, ≥6 ♂ (n=544)**	**p-value**	**%CDT ≤ 2.5 % (n=1562)**	**%CDT >2.5 % (n=486)**	**p-value**
Neurology/ neurosurgery	272 (25.3)	160 (29.4)	p=0.081	497 (31.8)	139 (28.6)	p=0.181
Respiratory failure	128 (11.9)	37 (6.8)	p=0.001*	151 (9.7)	40 (8.2)	p=0.342
Gastroenterology	75 (7.0)	51 (9.4)	p=0.091	77 (4.9)	49 (10.1)	p<0.001*
Traumatology	125 (11.6)	90 (16.5)	p=0.006*	200 (12.8)	57 (11.7)	p=0.532
Circulatory failure	148 (13.8)	49 (9.0)	p=0.005*	210 (13.4)	58 (11.9)	p=0.389
Sepsis	39 (3.6)	11 (2.0)	p=0.077	32 (2.0)	10 (2.1)	p=0.990
Intoxication, substance abuse	36 (3.4)	84 (15.4)	p<0.001*	101 (6.5)	59 (12.1)	p<0.001*
Other	250 (23.3)	62 (11.4)	p<0.001*	294 (18.8)	74 (15.2)	p=0.071

Categorical data are presented as absolute numbers and percentages and compared using the Chi-square test.

%CDT, carbohydrate-deficient transferrin; AUDIT-C, Alcohol Use Disorders Identification Test Consumption.

Table 3. Univariate analysis of variables associated with ICU-, hospital- and 3-year mortality. Variables were chosen to multivariate analysis if p<0.2 (indicated with *).

All n=1615	**ICU non-survivors n(%)**	**p**	**Hospital non-survivors n(%)**	**p**	**3-year non-survivors n(%)**	**p**
Operative n=523	34 (6.5)	0.567	50 (9.6)	0.013*	170 (32.5)	0.913
Nonoperative n=2009	145 (7.2)		274 (13.6)		648 (32.3)	
Emergency n=2360	179 (7.6)	<0.001*	322 (13.6)	<0.001*	765 (32.4)	0.665
Elective n=172	0 (0)		2 (1.2)		53 (30.8)	
Alcohol-related diagnosis n= 200	16 (8.0)	0.594	28 (14.0)	0.597	74 (37.0)	0.139
No alcohol-related diagnosis n= 2332	163 (7.0)		296 (12.7)		744 (31.9)	
Sex						
Men n=1605	117 (7.3)	0.567	215 (13.4)	0.233	540 (33.6)	0.058
Women n=927	62 (6.7)		109 (11.8)		278 (30.0)	
	ICU non-survivors vs survivors		**Hospital non-survivors vs survivors**		**3-year non-survivors vs survivors**	
Age, median (IQR)	68 (57-76) 60 (44-70)	<0.001*	68(58-76) 59 (43-69)	<0.001*	67 (58-76) 56 (39-67)	<0.001*
ICU LOS median (IQR)	0.96 (0.38-2.05) 1.42 (0.77-3.00)	<0.001*	1.34 (0.63-2.80) 1.37 (0.77-2.96)	0.076	1.55 (0.78-2.96) 1.30 (0.75-2.93)	0.126
SAPS II, median (IQR)	68 (54-78) 32 (21-45)	<0.001*	61 (50-73) 31 (20-44)	<0.001*	49 (35-63) 28 (19-40)	<0.001*
SOFA, median (IQR)	12 (10-15) 6 (3-9)	<0.001*	11 (9-14) 5 (3-8)	<0.001*	9 (6-11) 5 (3-8)	<0.001*
TISS sum, median (IQR)	87 (49-140) 66 (41-127)	0.004*	92 (55-158) 64 (41-124)	<0.001*	84 (51-151) 62 (39-120)	<0.001*
%CDT, median (IQR)	2.1 (1.8-2.6) 2.0 (1.7-2.5)	0.104	2.1 (1.8-2.7) 2.0 (1.7-2.5)	0.005*	2.0 (1.7-2.6) 1.9 (1.7-2.5)	0.014*
AUDIT C, median (IQR)	2 (0-6.75) 3 (0-7)	0.345	1 (0-6) 3 (0-6)	0.014*	2 (0-6) 3 (1-7)	0.001*

ICU, intensive care unit, IQR, Inter-quartile range; ICU LOS, Intensive Care Unit Length of Stay; SAPS II, Simplified Acute Physiology Score II; SOFA 24, Sequential Organ Failure Assessment score from 1st 24 hours in

ICU; TISS, Therapeutic Intervention Scoring System; %CDT, Carbohydrate deficient transferrin; AUDIT-C, Alcohol Use Disorders Identification Test Consumption.

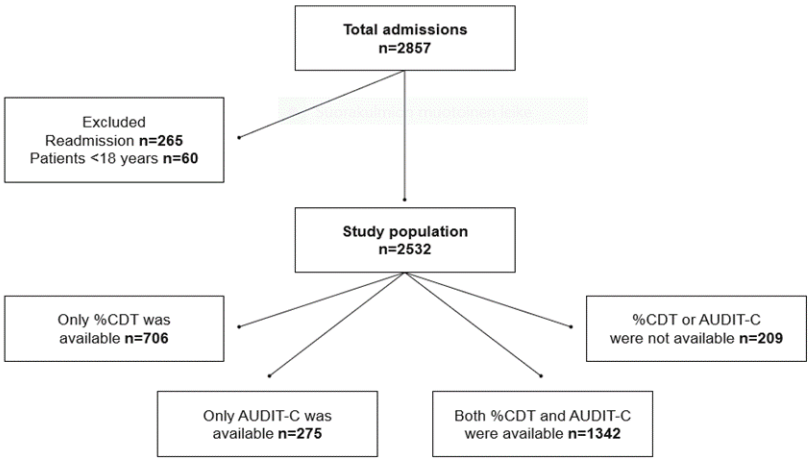

Figure 1. Study flowchart.

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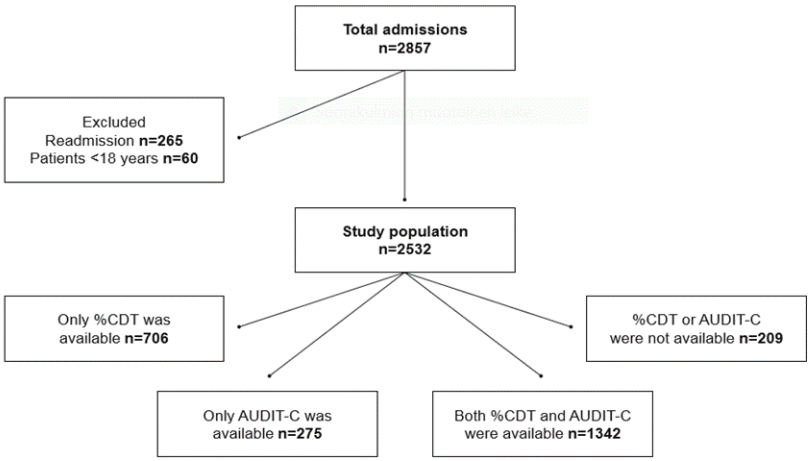

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2a. Female patients

2b. Male patients

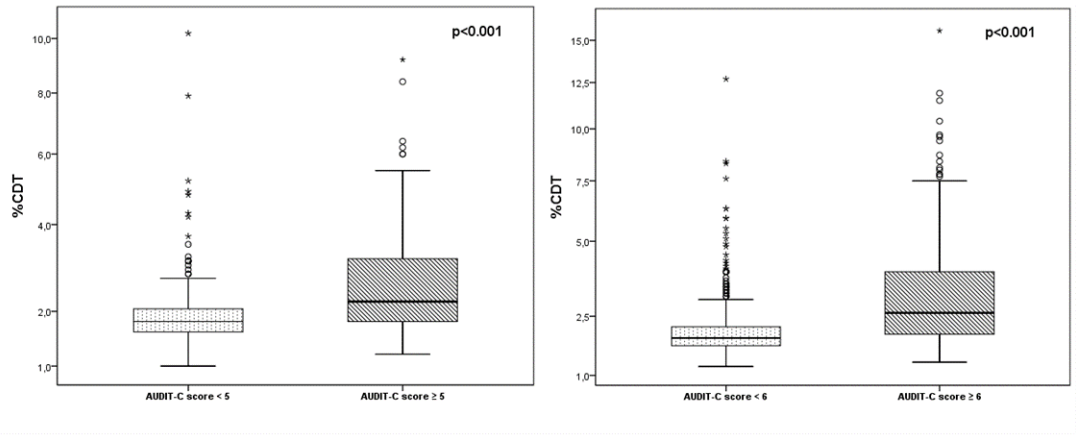

Figure 2. Distribution of %CDT for women and men by using AUDIT-C reference values.

%CDT, carbohydrate-deficient transferrin; AUDIT-C, Alcohol Use Disorders Identification Test, Consumption.

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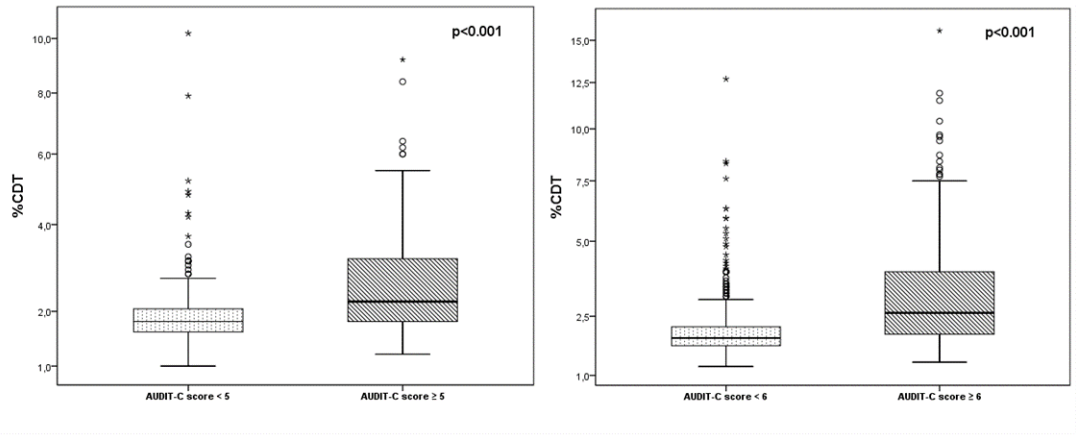
2a. Female patients

2b. Male patients



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